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Vaccine administration and the development of immune thrombocytopenic purpura in children

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The most important reasons cited by the opponents of vaccines are concerns about vaccine safety. Unlike issues such as autism for which no indisputable documentation of direct relationship with vaccine use is available, immune thrombocytopenic purpura (ITP) is an adverse event that can really follow vaccine administration, and may limit vaccine use because little is known about which vaccines it may follow, its real incidence and severity, the risk of chronic disease, or the possibility of recurrences after new doses of the same vaccine. The main aim of this review is to clarify the real importance of thrombocytopenia as an adverse event and discuss how it may interfere with recommended vaccination schedules. The available data clearly indicate that ITP is very rare and the only vaccine for which there is a demonstrated cause-effect relationship is the measles, mumps and rubella (MMR) vaccine that can occur in 1 to 3 children every 100,000 vaccine doses. However, also in this case, the incidence of ITP is significantly lower than that observed during the natural diseases that the vaccine prevents. Consequently, ITP cannot be considered a problem limiting vaccine use except in the case of children suffering from chronic ITP who have to receive MMR vaccine. In these subjects, the risk-benefit ratio of the vaccine should be weighed against the risk of measles in the community.

Introduction

Vaccines are the most beneficial and cost effective means of preventing infectious diseases as has been demonstrated by the worldwide eradication of smallpox, the widespread control of poliomyelitis, and significant reductions in the incidence of all of the diseases for which vaccines are available.[1,2] However, over the last 20–30 y, increasing numbers of parents in the industrialized world have chosen not to have their children vaccinated and, in some cases, even physicians themselves are uncertain as to whether to administer all of the recommended vaccinations to children.[3] The most important reasons cited by the opponents of vaccines are concerns about vaccine safety,[4] which is why vaccine safety is a priority of national immunization policies throughout the world, and every effort to clarify the type and the clinical importance of the really existing vaccine-related adverse events is recommended by health authorities.[5]

Thrombocytopenia is an adverse event that has been associated with vaccine administration, and may limit vaccine use because information regarding which vaccines it may follow, its real incidence and severity, the risk of chronic disease, or the possibility of recurrences after new doses of the same vaccine is poorly diffused among parents and a relevant number of physicians.

The main aim of this review is to clarify the real importance of thrombocytopenia as an adverse event and discuss how it may interfere with recommended vaccination schedules.

General Aspects of Thrombocytopenia Following Vaccine Administration

An international working group has recently defined thrombocytopenia as a clinical condition in which platelet counts are less than 100×10^9/L.[6] Vaccine-related thrombocytopenia is considered to be of immune origin because antibodies can be detected on platelets in about 79% of cases, which is why it is included among the secondary immune thrombocytopenias (ITPs) in the subgroup of drug-induced ITPs. Before this standardization, new cases of ITP were called acute ITP. However, because of this vagueness, this term was replaced by the definition of newly diagnosed ITP.[6] Patients in whom platelet counts remain lower than the lower normal limit 3–12 mo after diagnosis are considered as having persistent ITP,[6] and include those not achieving spontaneous remission and those not maintaining a response after stopping treatment. The term chronic ITP is reserved for patients with ITP lasting for more than 12 mo.[6] Regardless of the phase of the disease, the term severe ITP should only be used to describe patients with clinically relevant bleeding,[6] which is defined as the presence of bleeding symptoms at presentation sufficient to mandate treatment, or the occurrence of new bleeding symptoms requiring an additional therapeutic intervention with a different platelet-enhancing agent or an increased dose.

Thrombocytopenia following vaccine administration depends on the development of autoantibodies that cross-react with the naturally present antigenic targets on platelets.[7] It is more frequent in young children because their idiotypic network is still forming, and this increases the likelihood of post-vaccination, cross-reactive autoantibody expression.[8] It has also been suggested that

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defective immune regulation of genetic origin may play a role in the pathogenesis of the disease.[9]

Risk of ITP after Vaccination

There are few and not always reliable data concerning the absolute risk of developing ITP in children receiving any type of vaccine. Reports from surveillance systems are subject to substantial reporting bias as reporting depends on the vaccination schedule used in each country: for example, there are limited data regarding hepatitis B vaccine (HB) because it is not universally recommended for children in some industrialized countries. Moreover, the diagnosis of ITP is often not adequately confirmed, the presence of concomitant clinical conditions such as viral infections that may be associated with thrombocytopenia is not systematically evaluated, the frequent administration of combined vaccines hinders the evaluation of the importance of the individual preparations, and healthcare providers may over-report ITP when it occurs after the administration of measles, mumps and rubella (MMR) vaccine (the only vaccine for which an association is widely documented).

Furthermore, the data coming from surveillance systems seem to suggest that the relevance of ITP after vaccination is modest in terms of frequency and severity. Between 1992 and 2007, only 115 cases of ITP were reported in Canada, 77 of which (74.7%) occurred after MMR, 28 after diphtheria, tetanus and pertussis (DTP) or diphtheria, tetanus and acellular pertussis (DTaP) vaccine, and 10 after varicella (V) vaccine. Most of the cases were mild and did not give rise to severe complications.[10] Between 1990 and 2008, the US Vaccine Adverse Events Reporting System reported 478 cases of ITP after MMR alone or in combination with other vaccines, 47 cases after V, 32 after hepatitis A (HA) vaccine, and eight after DTaP, although practically all vaccines were associated with the development of ITP at least once.[11]

Despite the above-mentioned limitations, data from passive surveillance systems clearly indicate that the only vaccine for which there is a reliable relationship with the development of ITP is MMR. This is also supported by the data collected by Rajantie et al.[12] and O'Leary et al.[13] in studies specifically planned to evaluate the association between ITP and vaccine use. The first authors prospectively collected population data concerning 35 consecutive pediatric patients living in North European countries who presented ITP within one month of vaccination, and found that 24 had ITP after MMR, giving an estimated ITP risk of approximately 1 in 30,000 vaccine inoculations, a value significantly lower than that reported after natural infections.[12] O'Leary et al.[13] used data from five managed care organizations in the USA, identified 197 chart-confirmed ITP cases out of 1.8 million children, and confirmed that there was no high risk of ITP after any early childhood vaccine other than MMR in the 12–29 mo age group [95% confidence interval (CI) 1.61–18.64, p = 0.006].[13] They did find a significantly high risk of ITP after HA vaccine at 7–17 y of age (95% CI 3.59–149.30, p = 0.001), and after V and DTaP vaccine at 11–17 y of age (95% CI 1.10–133.96, p = 0.04; 95% CI 3.12–131.83, p = 0.002, respectively) but, because the association between ITP and vaccines other than MMR were based on only one or two vaccine-exposed cases, they suggested that these findings could only be considered a hypothesis rather than conclusive evidence, and suggested the need for further studies to clarify the question.[13]

MMR Vaccine-Associated ITP

The development of ITP after the administration of a live attenuated measles vaccine was first described by Oski and Naiman in 1966.[14] Since then, a number of reports have clearly demonstrated that all of the live, attenuated viruses in the MMR vaccine can cause ITP whether administered alone or in combination.[15-24] The hypothesis that MMR-related ITP may be due to a specific immunological mechanism is supported by the recent findings by Okazaki,[25] who detected anti-measles and anti-rubella virus IgG antibodies in platelets isolated from a 15-mo-old child who developed ITP after the sequential administration of MR, V and M vaccines separated by four weeks. The antibodies were found on day 154 of illness when the platelet count was very low but were no longer detectable on day 298 (at the end of the period of thrombocytopenia) or on day 373, when the disease was cured.[25]

A recently published systematic review of 12 studies has found that the likelihood of developing ITP after MMR vaccination is approximately 2.6/100,000 vaccine doses (range 0.087–4).[21] Although this probably does not really reflect the real incidence of the disease because mild cases without bleeding are not likely to come to medical attention, post-MMR vaccine ITP is probably significantly less common than the same disease after one of the three preventable natural infections.[21] It has been estimated that the incidence of ITP after rubella is 1/3,000 and that it is even higher after measles.[26] The risk of ITP after natural rubella infection ranges from 6 to 1,200/100,000, which means that the highest reported incidence of MMR-associated ITP (4/100,000) is 50% lower than the lowest reported incidence of rubella-associated ITP (6/100,000). The absence of any overlap in these figures indicates that the difference in the absolute frequency of the two forms of ITP is statistically significant. This is in line with what has been found in the case of all of the other clinical manifestations of the threes viruses, which are significantly more frequent and severe when the viruses cause a natural infection than when they are administered in attenuated form with the vaccine.[27]

MMR vaccine-related ITP usually occurs within six weeks of vaccination. In most cases, it is mild and presents with only bruising and petechiae.[17] Platelet counts are higher than in the case of non-vaccine-associated ITP (> 20,000 × 10^9/L in 33–19% of patients).[28] Serious bleeding requiring hospitalization and/or transfusion is exceptional,[13] although gastrointestinal hemorrhage,[23] hematuria,[19] pulmonary hemorrhage,[23] and a need for splenectomy[16] have been described in isolated cases. No deaths strictly related to IPT following MMR vaccine have ever been reported.[23] One case of lethal intracranial hemorrhage was not spontaneous but related to a closed head injury.[29] In most cases, the thrombocytopenia resolves in a few days or weeks. More than 90% of children are completely cured within six months of diagnosis, and less than 10 %develop chronic disease.[18,19,23,29] France et al. found that among children aged 12–23 mo with ITP, the

percentage of those who had developed chronic disease was quite similar among those who had been vaccinated and those who had not (10% vs. 7%).[18] Consequently, the prognosis is significantly better than that of the ITP following viral infections, which becomes chronic in 25–28% of cases.[6] The administration of MMR vaccine to children with a history of non-vaccine or MMR-associated ITP but a normal number of platelets at the time of vaccination seems to be safe and well tolerated. Although there have been reports of isolated cases of relapse,[30,31] recent studies indicate that the first dose of MMR does not generally reactivate previous acute ITP. Moreover, booster doses are not followed by recurrences within six weeks of administration. The question of administering MMR vaccine to children with chronic ITP has been less widely studied, but Bibby et al.[32] have described three cases of children with persistently low platelet counts who received it without any major clinical problem, although the platelet levels of two slightly decreased further.

In conclusion, although MMR vaccine is associated with an increased risk of thrombocytopenia, the risk is lower than that due to the wild viruses, and the clinical picture is less severe. On the basis of these findings, the potential severity of these vaccine-preventable diseases (particularly measles), and the fact that the persistent circulation of wild viruses leads to periodic epidemics, most of the experts think there is no need to limit the use of MMR vaccine.[12,13,17] The same seems to be true in the case of children who have previously developed ITP but who are in remission at the time of vaccination.[12,13,17] Children with chronic ITP require a more cautious approach: for example, the British Committee for Standards in Haematology advises measuring measles titers before booster administration in order to decide whether a further dose is indicated. If a child has not been previously immunized, the risk-benefit ratio of MMR should be weighed against the risk of measles in the community at the time.[33]

ITP and Other Vaccines

HB vaccine is another vaccine for which substantial data are available regarding a possible association with the development of ITP. The first description of ITP occurring suspiciously soon after the administration of HB vaccine was published in 1994, and related to a patient who took no other drugs and had no history of viral or bacterial infections.[34] Since then, a number of other cases have been reported,[35] although some of them may have been due to alternative reasons such as the concomitant administration of drugs.[36] There are no data concerning the absolute risk of developing ITP after HB vaccine administration but, as millions of doses have administered to children in some countries and there are only a few published cases of HB vaccine-associated ITP, it is reasonable to think that the risk is marginal. In the reported cases, ITP occurred between a few days and about three months after vaccine administration. As in the case of MMR vaccine, the clinical manifestations were mild and severe complications were rare, although treatment with corticosteroids, high-dose intravenous immunoglobulin or both may have significantly influenced the course of the disease in many patients.[35] Chronic disease is possible, but the real risk is unknown. ITP can be seen after any dose of HB vaccine. Consequently, although it has been suggested that repeated doses may boost autoantibody formation and that care is required when administering a booster dose to a patient developing ITP after the first dose,[36] HB vaccine can be given at any moment provided the number of platelets is in the normal range. However, vaccination in the presence of chronic ITP needs to evaluated in the light of the risk of HB infection.

Some cases of ITP have also been reported after the administration of V vaccine,[11,13,37] although sometimes only because the temporal relationship between the two events. As natural infection with varicella-zoster virus can be followed by thrombocytopenia and V vaccine is based on live attenuated viruses, it is not surprising that ITP may be associated with V vaccine. A study of the severe manifestations of varicella-zoster virus infection performed in Canada has found that the incidence of thrombocytopenia seems to be age-related as it was significantly higher in subjects aged more than 18 y.[38] This seems to be in line with data collected by O'Leary et al.,[13] who found an increased risk of ITP after V vaccine only in older children. As V vaccine is usually administered to younger children, the available data seem to indicate that it is not necessary to limit its use because of the risk of ITP. However, V vaccine is often administered together with MMR in a quadrivalent vaccine, and there is a need for further studies of this combined preparation.

Trivalent inactivated influenza vaccine (TIV) has been associated with ITP in a very small number of adult case reports,[39-44] and a recently published surveillance study of adults in Germany considered that three out of 169 cases of ITP were probably associated with the use of TIV.[45] The incidence seems to be even lower in children. The only published pediatric case report is that of Mantadakis et al.,[46] who described a previously healthy 3-y-old boy who developed ITP 26 d after immunization with the second dose of TIV. He recovered quickly and uneventfully within two days of receiving a single dose of intravenous immunoglobulin. Surveillance studies of vaccine safety including children and studies of ITP cases associated with drug administration also indicate a marginal incidence of TIV-related ITP.[10,11,47] Moreover, ITP has never been described after the administration live attenuated influenza vaccine to children.[48] On the contrary, symptomatic thrombocytopenia occurs in a substantial number of children and adults requiring hospitalization because of complicated natural influenza, in the case of seasonal virus infection.[49-51] As the risk of ITP seems to be seems to be significantly higher after natural influenza than after immunization, annual influenza vaccination can be administered without restrictions to all children in accordance with the official recommendations of each country.

There are few data regarding the other vaccines currently recommended for children, and those that do exist frequently relate to case reports in which the relationship between ITP and vaccine administration is not definite. Consequently, there is no need to limit their use for fear of ITP. However, particularly for those vaccines that have been only recently marketed, accurate surveillance has to be planned in order to clearly evaluate the possible emergence if ITP after single vaccine administration. This to avoid the risk that misconceptions regarding these new prophylactic measures could arise.

Conclusions

Although the administration of vaccines can be followed by the development of ITP, this analysis of the available data clearly shows that this is very rare. The only vaccine for which there is a demonstrated cause-effect relationship is MMR but, also in this case, the incidence of ITP is significantly lower than that observed during the natural course of the diseases that the vaccine prevents. Consequently, ITP, regardless of whether or not linked to vaccination, should not be considered a problem limiting the use of vaccine. Care is required only in the case of children with persistent or chronic ITP who need to receive MMR: in these subjects, the risk of vaccine administration should be weighed against the risk of measles in the area where they live. However, studies particularly for the new vaccines have to be planned and researches to find new methods of developing vaccines that do not carry any risk for ITP are needed. Reverse vaccinology and preparation of protein vaccines can be a reasonable target at this regard.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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